Complete Summary

GUIDELINE TITLE

Dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support in the first-line treatment of advanced or metastatic adult soft tissue sarcoma: a practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M, Sarcoma Disease Site Group. Dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support in the first-line treatment of advanced or metastatic adult soft tissue sarcoma: a practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr 11. 24 p. (Evidence-based series; no. 11-5). [41 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Inoperable locally advanced or metastatic soft tissue sarcoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate whether first-line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation improves response rate, time-to-disease progression, or survival, compared with standard-dose chemotherapy in patients with inoperable locally advanced or metastatic soft tissue sarcoma
- To evaluate the effects of first line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation on toxicity and quality of life

Note: For the purposes of this practice guideline, "dose-intensive chemotherapy" is defined as regimens administered with the intent to increase standard doses of chemotherapy, supported by the use of hematopoietic growth factors and/or autologous bone marrow/stem cell transplant support. Standard chemotherapy includes regimens that have been previously evaluated in a large phase II trial or a randomized phase III trial without growth-factor support.

TARGET POPULATION

Patients with inoperable locally advanced or metastatic soft tissue sarcoma

INTERVENTIONS AND PRACTICES CONSIDERED

1. Growth factor support in first line dose-intensive treatment with chemotherapy
2. Autologous bone marrow/stem cell transplantation support in first line dose-intensive treatment with chemotherapy

MAJOR OUTCOMES CONSIDERED

- Response rate
- Time-to-disease progression
- Survival
- Toxicity
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1982 to January Week 4, 2005), EMBASE (1980 to February Week 6, 2005), and the Cochrane Library (2005, Issue 1) databases were searched. Disease-specific search terms "sarcoma" (Medical subject heading [MeSH]), "soft tissue neoplasms" (MeSH), "*sarcoma/dt" (exploded MeSH term) and "soft tissue sarcoma" (text word) were combined with treatment-specific terms "drug therapy" (MeSH), "drug therapy, combined" (MeSH), "granulocyte-macrophage colony-stimulating factor" (MeSH), "granulocyte colony-stimulating factor" (MeSH), "bone marrow transplantation" (MeSH), "transplantation, autologous" (MeSH), "hematopoietic stem cell transplantation" (MeSH) and each of the following phrases used as text words: "chemotherapy," "high-dose," "dose-intense," "g-csf," "gm-csf," "growth factor," "abmt," "pbsc," "psct," "transplant". These terms were combined with search terms for the following publications types: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, phase I clinical trials, phase II clinical trials, and phase III clinical trials.

In addition, the 1998-2004 conference proceedings of the American Society of Clinical Oncology (ASCO) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Inclusion Criteria

Articles (full reports or abstracts) were eligible for inclusion in this systematic review of the evidence if they matched one of the following sets of criteria:

1. They were first line randomized controlled trials (RCTs) comparing dose-intensive chemotherapy regimens, supported by growth factor (e.g., granulocyte-colony stimulating factor [G-CSF] or granulocyte-macrophage colony stimulating factor GM-CSF) or autologous bone marrow/stem transplantation, with a lower- or standard-dose chemotherapy regimen in adult patients with locally advanced or metastatic soft tissue sarcoma (STS). They reported data, by allocation group, on overall survival, time-to-progression, or tumour response rate. "Dose-intensive chemotherapy" was

defined as regimens for which the investigators expressed intent to increase standard doses of chemotherapy supported by the use of hemopoietic growth factors and/or autologous bone marrow/stem cell transplant support. Comparator regimens were accepted as standard chemotherapy if they had been previously evaluated in a large phase II trial or a randomized phase III trial without growth-factor support.

2. First-line single-arm non-comparative trials were also included if they were phase II trials that reported toxicity data, response rates, or survival rates or if they were phase I trials that reported dose-limiting toxicity (DLT) or maximum tolerable dose (MTD) for adult patients who received dose-intensive chemotherapy (as defined above) as first-line therapy for locally advanced or metastatic STS. The rationale for including the non-comparative trials was due to the paucity of randomized controlled trials and to permit as detailed a description as possible of the potential efficacy and toxicity of dose-intensive chemotherapy in STS.

Exclusion Criteria

Articles were excluded from the systematic review if:

1. They included patients with pediatric sarcomas, bone sarcoma, or small round cell sarcomas including Ewing's sarcoma.
2. They assessed dose-intensive chemotherapy in the second-line setting.
3. They were letters or editorials.
4. They were published in a language other than English.

NUMBER OF SOURCE DOCUMENTS

Two phase III randomized trials, 12 phase II trials, and 5 phase I dose-escalation trials were reviewed

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Synthesizing the Evidence

The Disease Site Group (DSG) considered pooling data from relevant randomized trials but decided that meta-analysis would not be appropriate because the two

phase III trials found by the literature search evaluated different chemotherapy regimens.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This systematic review was developed by Cancer Care Ontario's (CCO's) Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development. Evidence was selected and reviewed by two members of the PEBC Sarcoma Disease Site Group (DSG) and methodologists.

The series is a convenient and up-to-date source of the best available evidence on dose-intensive chemotherapy for patients with inoperable locally advanced or metastatic soft tissue sarcomas (STS), developed through systematic review, evidence synthesis, and input from practitioners in Ontario. This evidence-based series has been reviewed and approved by the Sarcoma DSG, which comprises medical oncologists, radiation oncologists, surgeons, a pathologist, a methodologist and community representatives.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to the submission of this Evidence-based Series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel were that a recommendation around the use of stem cell transplantation cannot be made given that insufficient data exists and that the recommendation did not specify the first-line treatment setting and questioned the inclusion of phase I and phase II trials assessing growth factors, given the availability of the randomized controlled trials (RCTs).

To address the key RAP comments, the Disease Site Group (DSG) created two separate recommendations, with one stating that a recommendation to support the use of bone marrow or stem cell transplantation could not be made due to insufficient data. The inclusion of "first-line" was incorporated into the recommendations. The inclusion of the phase I and phase II trials was in part a reflection of the past practice of including those trial types and in part due to the DSG's desire to provide a detailed description of the efficacy and toxicity of the treatments.

External Review

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Sarcoma DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Feedback was obtained through a mailed survey of 74 practitioners in Ontario, which included medical oncologists, radiation oncologists, and surgeons. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on February 22, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Sarcoma Disease Site Group reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Dose-intensive chemotherapy with growth factor support is not recommended in the first-line treatment of patients with inoperable locally advanced or metastatic soft tissue sarcoma.
- There is insufficient data to support the use of high-dose chemotherapy with autologous bone marrow/stem cell transplantation as first-line treatment in this group of patients.
- Eligible patients should be encouraged to enter clinical trials assessing novel approaches or compounds.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by Phase III randomized trials, Phase II trials, and Phase I dose-escalation trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One randomized trial (N=314) did not detect significant differences in response rate (p=0.65) or survival (log-rank p=0.98) between high-dose doxorubicin (75 mg/m^2) plus ifosfamide (5 g/m^2) with granulocyte-macrophage colony stimulating factor (GM-CSF) and doxorubicin (50 mg/m2) plus ifosfamide (5 g/m^2) at standard doses. Progression-free survival, however, was significantly longer in the high-dose arm (log-rank p=0.03).
- Four phase II trials of high-dose regimens that contained ifosfamide (>7.5 g/m^2/per cycle) and an anthracycline observed tumour response rates in excess of 50%.

POTENTIAL HARMS

- One randomized trial reported higher rates of thrombocytopenia, infection, grade 3/4 asthenia, and grade 3/4 stomatitis with high-dose chemotherapy compared to standard-dose chemotherapy.
- Dose-liming toxicity for the dose-intensive chemotherapy regimens evaluated in phase I trials included neutropenia, thrombocytopenia, mucositis, neutropenic fever, vomiting, fatigue, and nephrotoxicity.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- High-dose chemotherapy with growth factor or autologous bone marrow/stem cell transplantation and standard-dose chemotherapy have similar adverse effects. The incidence of grade 3/4 thrombocytopenia is significantly higher; neutropenic fever and febrile neutropenia occur more frequently with high-dose regimens. Compared to standard treatment, the rate of treatment related deaths is also higher with high-dose regimens.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M, Sarcoma Disease Site Group. Dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support in the first-line treatment of advanced or metastatic adult soft tissue sarcoma: a practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr 11. 24 p. (Evidence-based series; no. 11-5). [41 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Apr 11

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Sarcoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Sarcoma Disease Site Group (DSG) disclosed potential conflicts of interest relating to the topic of this practice guideline. No potential conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support in the first-line treatment of advanced or metastatic adult soft tissue sarcoma: a practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Apr 11. Various p. (Practice guideline; no. 11-5). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 22, 2006. The information was verified by the guideline developer on July 6, 2006.

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